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         (c) 2002  Thomson Derwent
File 440:Current Contents Search(R) 1990-2002/Jul 17
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?t2/3 ab/1-26
>>>No matching display code(s) found in file(s): 65, 342

 2/AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13251915   22053472   PMID: 12058057
     Thrombospondin       2    Inhibits  Microvascular  Endothelial  Cell
 Proliferation  by a Caspase-independent Mechanism.
  Armstrong  Lucas  C; Bjorkblom Benny; Hankenson Kurt D; Siadak Anthony W;
Stiles Charlotte E; Bornstein Paul
  Department of Biochemistry, University of Washington, Seattle, Washington
98195.
  Molecular  biology  of  the  cell (United  States)   Jun  2002,  13   (6)
 p1893-905,  ISSN 1059-1524   Journal Code: 9201390
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: In Process
  The  matricellular  protein   thrombospondin    2   ( TSP2 ) regulates a
variety  of  cell-matrix  interactions.  A prominent feature of  TSP2 -null
mice is increased microvascular density, particularly in connective tissues
synthesized  after  injury.  We  investigated  the  cellular  basis for the
regulation  of  angiogenesis  by  TSP2  in  cultures  of murine and human
fibroblasts  and  endothelial  cells.  Fibroblasts isolated from murine and
human  dermis  synthesize  TSP2  mRNA  and secrete significant amounts of
immunoreactive  TSP2 , whereas endothelial cells from mouse lung and human
dermis  did  not synthesize  TSP2  mRNA or protein. Recombinant mouse  TSP2
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inhibited growth of human microvascular endothelial cells (HMVECs) mediated by basic fibroblast growth factor, insulin-like growth factor-1, epidermal growth factor, and vascular endothelial growth factor (VEGF). HMVECs exposed to TSP2 in the presence of these growth factors had a decreased proportion of cells in S and G(2)/M phases. HMVECs cultured with a combination of basic fibroblast growth factor, insulin-like growth factor-1, and epidermal growth factor displayed an increased proportion of nonviable cells in the presence of TSP2 , but the addition of VEGF blocked this TSP2 -mediated impairment of cell viability. TSP2 -mediated inhibition of DNA synthesis by HMVECs in the presence of VEGF was not affected by the broad-spectrum caspase inhibitor zVAD-fmk. Similar findings were obtained with TSP1. Taken together, these observations indicate that either TSP2 or TSP1 can inhibit HMVEC proliferation by inhibition of cell cycle progression and induction of cell death, but the mechanisms responsible for TSP2 -mediated inhibition of cell cycle progression are independent from those leading to cell death.

2/AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13191523 21977653 PMID: 11980922
Interactions of thrombospondins with alpha4beta1 integrin and CD47 differentially modulate T cell behavior.
Li Zhuqing; Calzada Maria J; Sipes John M; Cashel Jo Anne; Krutzsch Henry C; Annis Douglas S; Mosher Deane F; Roberts David D
Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892-1500, USA.
Journal of cell biology (United States) Apr 29 2002, 157 (3) p509-19 , ISSN 0021-9525 Journal Code: 0375356
Contract/Grant No.: HL54462; HL; NHLBI; HL56396; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Thrombospondin (TSP)-1 has been reported to modulate T cell behavior both positively and negatively. We found that these opposing responses arise from interactions of TSP1 with two different T cell receptors. The integrin alpha4beta1 recognizes an LDVP sequence in the NH2-terminal domain of TSP1 and was required for stimulation of T cell adhesion, chemotaxis, and matrix metalloproteinase gene expression by TSP1. Recognition of TSP1 by T cells depended on the activation state of alpha4beta1 integrin, and TSP1 inhibited interaction of activated alpha4beta1 integrin on T cells with its counter receptor vascular cell adhesion molecule-1. The alpha4beta1 integrin recognition site is conserved in TSP2 . A recombinant piece of TSP2 containing this sequence replicated the alpha4beta1 integrin-dependent activities of TSP1. The beta1 integrin recognition sites in TSP1, however, were neither necessary nor sufficient for inhibition of T cell proliferation and T cell antigen receptor signaling by TSP1. A second TSP1 receptor, CD47, was not required for some stimulatory responses to TSP1 but played a significant role in its T cell antigen receptor antagonist and antiproliferative activities. Modulating the relative expression or function of these two TSP receptors could therefore alter the direction or magnitude of T cell responses to TSPs.

2/AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12908603 21862939 PMID: 11874233
The secreted protein thrombospondin 2 is an autocrine inhibitor of

marrow stromal cell proliferation .
Hankenson Kurt D; Bornstein Paul
Department of Biochemistry, University of Washington, Seattle 98195-7350, USA.
Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research (United States) Mar 2002, 17 (3) p415-25, ISSN 0884-0431 Journal Code: 8610640
Contract/Grant No.: AR45418; AR; NIAMS; DE07063; DE; NIDCR; HL18645; HL; NHLBI; RR0161; RR; NCRR
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Marrow stromal cells (MSCs) are obtained in increased number from mice in which the thrombospondin 2 (TSP2) gene is disrupted, and these cells show increased DNA synthesis in vitro. To examine more closely the role of TSP2 in the physiology and osteogenic differentiation of MSCs, an in-depth characterization of TSP2 -null MSCs was conducted. Determination of TSP2 protein content by Western analysis and RNA levels by reverse-transcription polymerase chain reaction (RT-PCR) indicated that MSCs are the primary source of TSP2 in the marrow and secrete abundant TSP2 into culture medium. Morphologically, the TSP2 -null and wild-type (WT) cell populations were similar and by flow cytometry contained equivalent numbers of CD44+, Mac1+, intercellular adhesion molecule-1 (ICAM-1+), and ScaI+ cells. TSP2 -null cells showed delayed mineralization associated with an increased rate of proliferation. Consistent with this finding, there was a decrease in expression of collagen and osteocalcin RNA by TSP2 -null MSCs on day 7 and increased osteopontin expression on day 7 and day 14. In add-back experiments, recombinant TSP2 produced a dose-dependent decrease in proliferation. This reduction was associated with an accumulation of TSP2 -treated cells in the G1 phase of the cell cycle and did not result from an increase in apoptosis. When TSP2 treatment was terminated, the cell population reentered the S phase. We conclude that the increased endosteal bone formation observed in TSP2 -null mice results primarily from the failure of TSP2 to regulate locally MSC cell cycle progression.

2/AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11161624 21214514 PMID: 11314051
Transcription factor ATF3 partially transforms chick embryo fibroblasts by promoting growth factor-independent proliferation.
Perez S; Vial E; van Dam H; Castellazzi M
Unite de Virologie Humaine, Institut National de la Sante et de la Recherche Medicale (INSERM-U412), Ecole Normale Superieure, 46 allee d'Italie, 69364 Lyon Cedex 07, France.
Oncogene (England) Mar 1 2001, 20 (9) p1135-41, ISSN 0950-9232 Journal Code: 8711562
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Activating Transcription Factor 3 (ATF3) is a member of the bZip family of transcription factors. Previous studies in mammalian cells suggested that like other bZip family members e.g. Jun and Fos, ATF3 might play a role in the control of cell proliferation and participate in oncogenic transformation. To investigate this putative ATF3 function directly, the rat ATF3 protein was compared with v-Jun for its ability to transform primary cultures of chick embryo fibroblasts (CEFs). Like CEFs accumulating

v-Jun, CEFs accumulating the ATF3 protein displayed a typical, fusiform morphology, associated with an enhanced capacity to grow in medium with reduced amount of serum. However, in contrast to v-Jun-transformed CEFs, the ATF3 overexpressing cells could not promote colony formation from single cells in agar. Partial transformation induced by ATF3 was found to be associated with repression of multiple cellular genes that are also down-regulated by v-Jun, including those coding for the extracellular components fibronectin, decorin, thrombospondin 2 , and the pro-apoptotic protein Par-4. These data demonstrate that, at least in primary avian cells, rat ATF3 possesses an intrinsic oncogenic potential. Moreover, the results suggest that ATF3 might induce growth factor independence by down-regulating a subset of the genes repressed by v-Jun.

2/AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11034521 20583893 PMID: 11150912
Thrombospondin-1 and -2 in node-negative breast cancer: correlation with angiogenic factors, p53, cathepsin D, hormone receptors and prognosis.
Gasparini G; Toi M; Biganzoli E; Dittadi R; Fanelli M; Morabito A; Boracchi P; Gion M
Division of Medical Oncology, Azienda Complesso Ospedaliero 'San Filippo Neri', Rome, Italy.
Oncology (SWITZERLAND) 2001, 60 (1) p72-80, ISSN 0030-2414
Journal Code: 0135054
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
OBJECTIVE: Thrombospondins (TSP(s)) are a multigene family of five secreted glycoproteins involved in the regulation of cell proliferation , adhesion and migration. Two members of the TSP family, namely TSP-1 and TSP - 2 , are also naturally occurring inhibitors of angiogenesis. The aim of the present study was to determine the prognostic significance of the determination of TSP-1 and -2 and their correlation with the angiogenic peptides vascular endothelial growth factor (VEGF) and thymidine phosphorylase (TP), as well as with other biological and clinicopathological features investigated. METHODS: We evaluated a series of 168 women with node-negative breast cancer with a median follow-up period of 66 months, not treated with adjuvant therapy. The cytosolic levels of TSP-1 and -2 were determined in the primary tumour by a commercially available immunometric assay. RESULTS: We found that 166 tested tumours had measurable levels of TSP-1 and -2 protein (median value 5.978, range 0.579-31.410 ng/mg of protein). On the basis of Spearman's rank correlation coefficient, a weak inverse association of TSP-1 and -2 with tumour size and cathepsin D was found. Moreover, principal component analysis on ranks evidenced a poor association between TSP-1 and -2, VEGF and TP. The results of the clinical outcome were analysed by both univariate and multivariate [for relapse-free survival (RFS) only]) Cox regression models. TSP-1 and -2 were not significant prognostic factors in univariate analysis for either RFS (p = 0.427) or overall survival (p = 0.069). To investigate the 'angiogenic balance hypothesis', bivariate analyses were performed to investigate the interactions of TSP-1 and -2 with VEGF, TP or p53, but none were included in the selected models. Finally, in multivariate analysis for RFS a baseline model, previously defined in a larger case series and inclusive of VEGF, TP and their interaction was adopted. It was highly significant (p = 0.002, Harrell c statistic value of 0.703); but when TSP-1 and -2 were added, their contribution was negligible (p = 0.731, Harrell c statistic value of 0.705). CONCLUSIONS: The results of this study suggest that TSP-1 and -2 do

not provide additional prognostic contribution to the joint effects of VEGF and TP. In the series of node-negative breast cancer patients investigated, determination of the angiogenic peptides VEGF and TP gave significant prognostic information. On the contrary, TSP-1 and -2, potential naturally occurring negative regulators of angiogenesis, lacked prognostic value.

2/AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10514714 20038258 PMID: 10568831
Expression of angiostatic factors in colorectal cancer.
Yoshida Y; Oshika Y; Fukushima Y; Tokunaga T; Hatanaka H; Kijima H; Yamazaki H; Ueyama Y; Tamaoki N; Miura S; Nakamura M
Department of Pathology, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa 259-1193, Japan.
International journal of oncology (GREECE) Dec 1999, 15 (6) p1221-5, ISSN 1019-6439 Journal Code: 9306042
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Angiogenesis plays an important role in growth and proliferation of cancer. Various angiogenic and angiostatic factors regulate angiogenesis. We examined expression of genes encoding various angiostatic factors: thrombospondin 1 (TSP1), thrombospondin 2 (TSP2), brain-specific angiogenesis inhibitor 1 (BAI1) and angiopoietin 2 (AGP2) in 62 colorectal cancers and 40 samples of extraneoplastic colon mucosa. The expression of the angiostatic factors TSP2 and AGP2 were significantly increased in the cancerous mucosa as compared to these in extraneoplastic mucosa (o2 test; p<0. 0001, and Fisher's exact test; p<0.0001), while the increase in TSP1 expression was not significant. BAI1 expression was slightly decreased in the cancer tissue. These results suggested that specific types of angiostatic factors might have protective roles against cancer cell proliferation via dormancy due to hyponutrition caused by decreased vascularity.

2/AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09932400 98357946 PMID: 9694573
Hormonally regulated components of the adrenocortical cell environment and the control of adrenal cortex homeostasis.
Feige J J; Keramidas M; Chambaz E M
INSERM Unite 244, Departement de Biologie Moleculaire et Structurale, CEA Grenoble, France. jjfeige@geant.ceng.cea.fr
Hormone and metabolic research. Hormon- und Stoffwechselforschung. Hormones et metabolisme (GERMANY) Jun-Jul 1998, 30 (6-7) p421-5, ISSN 0018-5043 Journal Code: 0177722
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The extracellular matrix (ECM) strongly contributes to the regulation of cell proliferation and cell differentiation, and thereby of embryonic development and adult tissue homeostasis. We review here the ongoing characterization of the structure and functions of the extracellular matrix components secreted by adrenocortical cells and discuss their possible implication in the hormonal regulation of adrenal cortex homeostasis. Fibronectin (FN) and laminin (LN) are both major adhesive proteins for

adrenocortical cells. FN is synthesized by bovine fasciculata cells in primary culture, and its synthesis is stimulated by TGF(beta)1, TGF(beta)2, and FGF-2 but is not modified by IGF-1 or by the hormones ACTH and angiotensin II. LN is also synthesized by bovine fasciculata cells and its synthesis is specifically stimulated by ACTH. Both proteins are haptotactic and chemotactic for adrenocortical cells, suggesting a physiological role in adrenocyte migration. Their distribution in the adrenal gland is quite distinct. LN is uniformly present in the steroidogenic cells from the three zones, whereas FN is abundant in the fibrovascular structures of the capsule and the cortex. ACTH treatment of adrenocortical cells strongly induces the expression and secretion of thrombospondin - 2 (TSP2), a large trimeric matricellular protein. The multimodular structure of TSP2 is the support of a variety of biological functions. TSP2 promotes attachment but prevents spreading of adrenocortical cells. On the other hand, TSP2 induces the activation of latent TGFbeta through an indirect mechanism and is anti-angiogenic in vitro. The overall distribution of TSP2 in the glomerulosa and fasciculata zones of the adrenal cortex, and its absence from the reticularis zone, argue in favor of a role in the protection of adrenocortical cells against apoptosis. In the adrenal cortex, five main biological functions are potentially regulated by components of the extracellular matrix : stem cell commitment into the adrenocyte differentiation pathway, terminal differentiation toward the three distinct adrenocyte phenotypes, centripetal migration, apoptosis and the formation of the capillary network. Future studies will aim at deciphering which extracellular component(s) is involved in each of these regulations.

2/AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09272550 97169050 PMID: 9016857
Endothelial cell mitogenesis induced by LPA: inhibition by thrombospondin-1 and thrombospondin - 2 .
Panetti T S; Chen H; Misenheimer T M; Getzler S B; Mosher D F
Department of Medicine, University of Wisconsin-Madison, 53706, USA.
Journal of laboratory and clinical medicine (UNITED STATES) Feb 1997, 129 (2) p208-16, ISSN 0022-2143 Journal Code: 0375375
Contract/Grant No.: HL 54462; HL; NHLBI; HL09150; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We examined the effects of thrombospondin-1 (TSP1) and thrombospondin - 2 (TSP2) on the uptake of tritiated thymidine by bovine aortic endothelial (BAE) cells in response to two growth factors, basic fibroblast growth factor (bFGF) and lysophosphatidic acid (LPA). bFGF and LPA stimulate cell proliferation through distinct receptors that have convergent signaling pathways. The doses of LPA that trigger proliferation of BAE cells, which have not been reported previously, were 1 to 30 micromol/L, as opposed to the 5 to 100 micromol/L concentrations required to stimulate proliferation of human foreskin fibroblasts. Baseline mitogenic activity and activity stimulated by either bFGF or LPA on BAE cells was inhibited by human TSP1 purified from platelets or a recombinant source with a similar dose response. These results demonstrate that the anti-proliferative effect of platelet TSP1 is not caused by contaminants from the stimulated platelet. Recombinant mouse TSP2 inhibited BAE cell proliferation in response to LPA in a dose range similar to that of TSP1. Inasmuch as TSP2 does not activate latent TGFbeta1 (Schultz-Cherry et al., J Biol Chem 1995;270: 7304), these results show that inhibition of angiogenesis by TSPs is not related to control of activation of TGFbeta.

Together, these studies suggest that structural motifs common to TSP1 and TSP2 inhibit endothelial cell proliferation . Furthermore, TSPs inhibit cell proliferation stimulated by two growth factor receptors that act through distinct signaling pathways.

2/AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08667245 96010271 PMID: 7573352
Expression of thrombospondins by endothelial cells. Injury is correlated with TSP-1.
Reed M J; Iruela-Arispe L; O'Brien E R; Truong T; LaBell T; Bornstein P; Sage E H
Department of Medicine, University of Washington, Seattle 98195, USA.
American journal of pathology (UNITED STATES) Oct 1995, 147 (4) p1068-80, ISSN 0002-9440 Journal Code: 0370502
Contract/Grant No.: AG00503; AG; NIA; HL18645; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The thrombospondins (TSP-1, -2, and -3) comprise a family of proteins that are homologous at the carboxy terminus but have unique sequences at the amino terminus that might be correlated with the regulation of cell behavior. To investigate the expression of TSP-1, -2, and -3 in endothelial cells, we examined developing murine blood vessels and human atherosclerotic plaques by in situ hybridization. The expression of TSP-1 was also characterized in cultured bovine aortic endothelial cells. Expression of TSP - 2 was seen in the dorsal aorta as early as embryonic day 10; TSP-1 was not detected in endothelial cells until later stages, and TSP-3 was not apparent in the vasculature. In atherosclerotic specimens, TSP-1 mRNA was detected in many intraplaque microvessels and in the endothelium lining the atheromatous plaque; TSP - 2 was absent from these regions. Cultured bovine aortic endothelial cells did not transcribe TSP - 2 mRNA at detectable levels. There were high steady-state levels of TSP-1 mRNA in subconfluent bovine aortic endothelial cells before confluence and at the wound edge after injury of the cell monolayer, with maximal expression of TSP-1 in cultures at a time during which approximately 35% of the cells were in S phase. As the majority of these cells subsequently undergo mitosis, these data are consistent with TSP-1 as an inhibitor of endothelial cell proliferation that functions in G1. These results support the conclusion that, despite sequence homology, the TSPs have distinct functions in vascular biology.

2/AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07222592 92147683 PMID: 1371115
Characterization of mouse thrombospondin 2 sequence and expression during cell growth and development.
Laherty C D; O'Rourke K; Wolf F W; Katz R; Seldin M F; Dixit V M
Department of Pathology, University of Michigan Medical School, Ann Arbor 48109.
Journal of biological chemistry (UNITED STATES) Feb 15 1992, 267 (5) p3274-81, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: DE-00301-01; DE; NIDCR; HG-00101; HG; NHGRI; HL-39037; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
Thrombospondin (TSP) is an extracellular matrix glycoprotein whose expression has been associated with a variety of cellular processes including growth and embryogenesis. The recent discovery of the existence of a second mouse TSP gene necessitates careful examination of the discrete biochemical and functional properties associated with each molecule. In this report, the primary structures of human TSP, mouse TSP1 (mTSP1), mouse TSP2 (mTSP2), and chicken TSP are compared; and the expression of mTSP1 and mTSP2 during embryogenesis and growth factor-mediated cell proliferation is examined. The cloning and sequencing of the entire coding regions of mTSP1 and mTSP2 revealed considerable conservation of residues critical for TSP structure and function; these data suggest that TSP2 is capable of trimer formation and many of the same cell-surface and ligand interactions that mediate TSP function. Comparison of the various TSP sequences also allowed the assignment based on sequence homology of previously reported human TSP as TSP1 and chicken TSP as TSP2 . mTSP2, like mTSP1, was shown to be a primary response gene when quiescent Swiss 3T3 cells were stimulated with serum, platelet-derived growth factor BB, basic fibroblast growth factor, or interleukin-1 beta. Interestingly, TSP1 and TSP2 exhibited markedly different tissue- and stage-specific patterns of mRNA expression during mouse embryogenesis, implying that the two TSP molecules possess discrete functional properties important for development. Additionally, the TSP genes (Thbs1 and Thbs2) were mapped to single loci on mouse chromosomes 2 and 17, respectively.

2/AB/11 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13536834 BIOSIS NO.: 200200165655
Thrombospondins: Multifunctional regulators of cell interactions.
BOOK TITLE: Annual Review of Cell and Developmental Biology
AUTHOR: Adams Josephine C(a)
BOOK AUTHOR/EDITOR: Schekman Randy; Goldstein Larry; McKnight Steven L; Rossant Janet: Eds
AUTHOR ADDRESS: (a)Department of Biochemistry and Molecular Biology, MRC Laboratory for Molecular Cell Biology, University College London, Gower Street, London, WC1E 6BT**UK E-Mail: dmcbjca@ucl.ac.uk
JOURNAL: Annual Review of Cell and Developmental Biology 17p25-51 2001
MEDIUM: print
BOOK PUBLISHER: Annual Reviews, 4139 El Camino Way, Palo Alto, CA, 94303-0139, USA
ISSN: 1081-0706 ISBN: 0-8243-3117-6 (cloth)
DOCUMENT TYPE: Book
RECORD TYPE: Citation
LANGUAGE: English
2001

2/AB/12 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13464799 BIOSIS NO.: 200200093620
Thrombospondin 2 is a paracrine, fibroblast-derived inhibitor of endothelial cell proliferation .
AUTHOR: Armstrong Lucas C(a); Hankenson Kurt D(a); Bjorkblom Benny(a); Siadek Anthony; Bornstein Paul(a)
AUTHOR ADDRESS: (a)Biochemistry, University of Washington, Seattle, WA,

98195**USA
JOURNAL: Molecular Biology of the Cell 12 (Supplement):p64a-65a Nov, 2001
MEDIUM: print
CONFERENCE/MEETING: 41st Annual Meeting of the American Society for Cell Biology Washington DC, USA December 08-12, 2001
ISSN: 1059-1524
RECORD TYPE: Citation
LANGUAGE: English
2001

2/AB/13 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13377693 BIOSIS NO.: 200200006514
Thrombospondin - 2 knockout mice show an accelerated response to injury in experimental glomerulonephritis.
AUTHOR: Daniel C(a); Bornstein P; Hugo C(a)
AUTHOR ADDRESS: (a)Department of Nephrology, University of Erlangen-Nuernberg, Erlangen**Germany
JOURNAL: Kidney & Blood Pressure Research 24 (4-6):p232 2001
MEDIUM: print
CONFERENCE/MEETING: Joint Scientific Meeting of the Nephrology Society and the German Working Group for Clinical Nephrology Munster, Germany September 29-October 02, 2001
ISSN: 1420-4096
RECORD TYPE: Citation
LANGUAGE: English
2001

2/AB/14 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13190617 BIOSIS NO.: 200100397766
Regulation of endothelial cell proliferation and apoptosis.
AUTHOR: Detmar Michael(a)
AUTHOR ADDRESS: (a)Harvard Medical School and Massachusetts General Hospital, Charlestown, MA**USA
JOURNAL: Skin Pharmacology and Applied Skin Physiology 14 (3):p141 May-June, 2001
MEDIUM: print
CONFERENCE/MEETING: 2nd Joint Meeting International Psoriasis Symposium and European Congress on Psoriasis San Francisco, California, USA June 19-24, 2001
ISSN: 1422-2868
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

2/AB/15 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09305989 Genuine Article#: 390BX Number of References: 48
Title: Thrombospondin-1 and-2 in node-negative breast cancer: Correlation with angiogenic factors, p53, cathepsin D, hormone receptors and

prognosis (ABSTRACT AVAILABLE)
Author(s): Gasparini G (REPRINT) ; Toi M; Biganzoli E; Dittadi R; Fanelli M ; Morabito A; Boracchi P; Gion M
Corporate Source: Azienda Complesso Osped San Filippo Neri,Div Med Oncol,Via Martinotti 20/I-00135 Rome//Italy/ (REPRINT); Azienda Complesso Osped San Filippo Neri,Div Med Oncol,I-00135 Rome//Italy/; Metropolitan Hosp,Dept Surg,Tokyo//Japan/; Ist Nazl Studio & Cura Tumori,Dept Med Stat & Biometry,I-20133 Milan//Italy/; Ctr Study Biol Markers Malignancy,Venice//Italy/; Univ Milan,Inst Med Stat & Biometry,Milan//Italy/
Journal: ONCOLOGY, 2001, V60, N1, P72-80
ISSN: 0030-2414 Publication date: 20010000
Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND
Language: English Document Type: ARTICLE
Abstract: Objective: Thrombospondins (TSPs) are a multigene family of five secreted glycoproteins involved in the regulation of cell proliferation , adhesion and migration. Two members of the TSP family, namely TSP-1 and TSP - 2 , are also naturally occurring inhibitors of angiogenesis. The aim of the present study was to determine the prognostic significance of the determination of TSP-1 and -2 and their correlation with the angiogenic peptides vascular endothelial growth factor (VEGF) and thymidine phosphorylase (TP), as well as with other biological and clinicopathological features investigated. Methods: We evaluated a series of 168 women with node-negative breast cancer with a median follow-up period of 66 months, not treated with adjuvant therapy. The cytosolic levels of TSP-1 and -2 were determined in the primary tumour by a commercially available immunometric assay. Results: We found that 166 tested tumours had measurable levels of TSP-1 and -2 protein (median value 5.978, range 0.579-31.410 ng/mg of protein). On the basis of Spearman's rank correlation coefficient, a weak inverse association of TSP-1 and -2 with tumour size and cathepsin D was found. Moreover, principal component analysis on ranks evidenced a poor association between TSP-1 and -2, VEGF and TP. The results of the clinical outcome were ana lysed by both univariate and multivarlate [for relapse-free survival (RFS) only]) Cox regression models. TSP-1 and -2 were not significant prognostic factors in univariate analysis for either RFS (p = 0.427) or overall survival (p = 0.069). To investigate the 'angiogenic balance hypothesis', bivariate analyses were performed to investigate the interactions of TSP-1 and -2 with VEGF, TP or p53, but none were included in the selected models. Finally, in multivariate analysis for RFS a baseline model, previously defined in a larger case series and inclusive of VEGF, TP and their interaction was adopted. It was highly significant (p = 0.002, Harrell c statistic value of 0.703); but when TSP-1 and -2 were added, their contribution was negligible (p = 0.731, Harrell c statistic value of 0.705). Conclusions: The results of this study suggest that TSP-1 and -2 do not provide additional prognostic contribution to the joint effects of VEGF and TP. In the series of node-negative breast cancer patients investigated, determination of the angiogenic peptides VEGF and TP gave significant prognostic information. On the contrary, TSP-1 and -2, potential naturally occurring negative regulators of angiogenesis, lacked of prognostic value. Copyright (C) 2001 S. Karger AG, Basel.

2/AB/16 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04508656 Genuine Article#: TJ020 Number of References: 24
Title: INHIBITION OF ANGIOGENESIS BY THROMBOSPONDIN - 2 (Abstract

Available)
Author(s): VOLPERT OV; TOLSMA SS; PELLERIN S; FEIGE JJ; CHEN H; MOSHER DF; BOUCK N
Corporate Source: NORTHWESTERN UNIV,SCH MED,DEPT MICROBIOL IMMUNOL/CHICAGO//IL/60611; NORTHWESTERN UNIV,SCH MED,DEPT MICROBIOL IMMUNOL/CHICAGO//IL/60611; NORTHWESTERN UNIV,SCH MED,RH LURIE CANC CTR/CHICAGO//IL/60611; CEN GRENOBLE,DEPT BIOL MOLEC & STRUCT/GRENOBLE//FRANCE/; UNIV WISCONSIN,DEPT MED/MADISON//WI/00000
Journal: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 1995, V217, N1 (DEC 5), P326-332
ISSN: 0006-291X
Language: ENGLISH Document Type: ARTICLE
Abstract: To assess the ability of proteins of the thrombospondin family to inhibit angiogenesis, recombinant murine thrombospondin - 2 , bovine thrombospondin - 2 /CISP and thrombospondin-5/COMP were purified and tested for ability to block the migration of capillary endothelial cells towards a variety of inducers and to inhibit neovascularization induced in the rat cornea. Both preparations of thrombospondin - 2 were active inhibitors in vitro and in vivo whereas thrombospondin-5/COMP was inactive. These results define thrombospondin - 2 as a newly identified naturally occurring inhibitor of angiogenesis and suggest that the properdin-like type 1 modules that it shares with antiangiogenic thrombospondin-1 and are missing in thrombospondin-5/COMP could contribute to this activity. (C) 1995 Academic Press,Inc.

2/AB/17 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01108368 Genuine Article#: FX132 Number of References: 38
Title: A 2ND, EXPRESSED THROMBOSPONDIN GENE (THBS2) EXISTS IN THE MOUSE GENOME (Abstract Available)
Author(s): BORNSTEIN P; OROURKE K; WIKSTROM K; WOLF FW; KATZ R; LI P; DIXIT VM
Corporate Source: UNIV MICHIGAN,SCH MED,DEPT PATHOL,1301 CATHERINE ST,BOX 0602/ANN ARBOR//MI/48109; UNIV MICHIGAN,SCH MED,DEPT PATHOL,1301 CATHERINE ST,BOX 0602/ANN ARBOR//MI/48109; UNIV WASHINGTON,DEPT BIOCHEM/SEATTLE//WA/98195
Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 1991, V266, N20, P12821-12824
Language: ENGLISH Document Type: NOTE
Abstract: The diverse and occasionally conflicting properties described for the extracellular, cell surface-associated protein thrombospondin (TSP) have raised the possibility that functionally distinct forms of the protein exist in the same organism. We have isolated and characterized a partial cDNA clone for mouse TSP that is clearly homologous to, but distinct from, the coding sequence for mouse TSP deduced from a mouse genomic clone (Bornstein, P., Alfi, D., Devarayalu, L., Framson, P., and Li, P. (1990) J. Biol. Chem. 265, 16691-16698). This second TSP, which we term thrombospondin 2 , is the product of a separate gene (Thbs2) and is expressed in a variety of mouse tissues in a pattern that differs from that for TSP1. Based on their translated amino acid sequences, it seems likely that TSP1 and TSP2 will be found to have both common and unique properties and that the functional consequences of TSP production will reflect the ratio of the levels of these two related proteins.

2/AB/18 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

11385288 EMBASE No: 2001399568
Thrombospondin-1 type 1 repeat recombinant proteins inhibit tumor growth through transforming growth factor-beta-dependent and -independent mechanisms
Miao W.-M.; Seng W.L.; Duquette M.; Lawler P.; Laus C.; Lawler J.
J. Lawler, Department of Pathology, Beth Israel Deaconess Medical Center, Research North, 99 Brookline Avenue, Boston, MA 02215 United States
AUTHOR EMAIL: jlawler@caregroup.harvard.edu
Cancer Research (CANCER RES.) (United States) 01 NOV 2001, 61/21 (7830-7839)
CODEN: CNREA ISSN: 0008-5472
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 50

Thrombospondin-1 (TSP-1) is a potent inhibitor of tumor growth and angiogenesis. The antiangiogenic activity of TSP-1 has been mapped to the procollagen homology region and the type 1 repeats (TSR) using synthetic peptides. To elucidate the molecular mechanisms that are involved in the inhibition of tumor growth by the TSRs, we have expressed recombinant versions of these motifs and have assayed their ability to inhibit the growth of experimental B16F10 melanomas and Lewis lung carcinomas. Recombinant proteins that contain all three TSRs (3TSR) or the second TSR with (TSR2+RFK) or without (TSR2) the transforming growth factor-beta (TGFbeta) activating sequence (RFK) have been expressed in Drosophila S2 cells. In addition, recombinant proteins with mutations in either the RFK sequence (TSR2+QFK) or the WSHWSPW sequence [TSR2 (W/T)] of the second TSR have been prepared. Similar to platelet TSP-1, these proteins are potent inhibitors of endothelial cell migration, and 3TSR of human TSP-1 (3TSR/hTSP-1) and TSR2+RFK activate TGFbeta. An 81% inhibition of B16F10 tumor growth is observed at 2.5 mg (135 nmol)/kg/day of the recombinant 3TSR/hTSP-1. A comparable level of inhibition is observed with 2.5 mg (360 nmol)/kg/day of TSR2+RFK. By contrast, 3TSR of mouse TSP - 2 (3TSR/mTSP-2), TSR2+QFK, and TSR2 are significantly less effective. TSR2+RFK and TSR2 reduce tumor vessel density, but TSR2+RFK has a greater effect on B16F10 tumor cell apoptosis and proliferation. Concurrent treatment of B16F10 tumor-bearing mice with TSR2+RFK and either a soluble form of the TGFbeta receptor or an antibody to active TGFbeta reduces the inhibition of BI6F10 tumor growth to levels that are comparable with those of TSR2 and TSR2+QFK. By contrast, the presence of the TGFbeta-activating sequence does not increase the level of inhibition of Lewis lung carcinoma experimental tumor growth. These data indicate that the TSRs inhibit tumor growth by inhibition of angiogenesis and regulation of tumor cell growth and apoptosis. The regulation of tumor cell growth and apoptosis is TGFbeta dependent, whereas the inhibition of angiogenesis is not.

2/AB/19 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

10967886 EMBASE No: 2001005614
The role of VEGF and thrombospondins in skin angiogenesis
Detmar M.
M. Detmar, Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129 United States
AUTHOR EMAIL: michael.detmar@cbrc2.mgh.harvard.edu
Journal of Dermatological Science (J. DERMATOL. SCI.) (Ireland) 2000 , 24/SUPPL. 1 (S78-S84)

CODEN: JDSCE ISSN: 0923-1811
PUBLISHER ITEM IDENTIFIER: S0923181100001456
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 30

The vasculature in adult skin remains normally quiescent, due to the dominant influence of endogenous angiogenesis inhibitors over angiogenic stimuli. However, skin retains the capacity for brisk initiation of angiogenesis, the growth of new blood vessels from preexisting vessels, during tissue repair and in numerous diseases, including inflammatory skin diseases such as psoriasis and skin cancers such as cutaneous squamous cell carcinomas. Moreover, cyclic vascular expansion occurs during the growth phase of the hair follicle. Recent evidence suggests vascular endothelial growth factor as the major skin angiogenesis factor. During skin angiogenesis, expression of vascular endothelial growth factor is induced in epidermal keratinocytes by several stimuli including transforming growth factor-alpha and hypoxia, leading to increased vascularization of the dermis. In contrast, vascular endothelial growth factor-C induces skin lymphangiogenesis. Thrombospondin-1 and thrombospondin - 2 are endogenous inhibitors of angiogenesis that are expressed in normal skin, maintaining the quiescence of cutaneous vessels. Both inhibitors potently inhibit skin cancer growth via inhibition of tumor angiogenesis. Targeting cutaneous blood vessels represents a promising new therapeutic approach for the treatment of a variety of skin diseases. (c) 2000 Elsevier Science Ireland Ltd.

2/AB/20 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06291387 EMBASE No: 1995328644
Thrombospondins selectively activate one of the two latent forms of transforming growth factor-beta present in adrenocortical cell-conditioned medium

Souchelnitskiy S.; Chambaz E.M.; Feige J.-J.
LBRCE, DBMS, Centre d'Etudes Nucleaires, 17 rue des Martyrs,F-38054 Grenoble Cedex 9 France

Endocrinology (ENDOCRINOLOGY) (United States) 1995, 136/11 (5118-5126)
CODEN: ENDOA ISSN: 0013-7227
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Transforming growth factor-beta (TGFbeta) has been shown previously to be a potent inhibitor of bovine adrenocortical cell steroidogenic functions. However, it is present in the culture medium of these cells in a latent form. In this study, we analyzed in detail the biochemical composition of this latent TGFbeta. Two distinct complexes could be separated chromatographically by gel filtration on Sephacryl S-300, and their composition was studied using immunochemical methods. The results indicate that one form (peak I) is a complex between alphainf 2-macroglobulin (alphainf 2M) and either the unprocessed TGFbeta precursor or the mature form of TGFbeta. In a major fraction of this complex, TGFbeta is covalently linked to alphainf 2M, whereas in a minor fraction, it is non- covalently bound and, therefore, activatable. The second form of latent TGFbeta (peak II) is a complex among latent TGFbeta-binding protein (LTBP), latency-associated protein, and mature TGFbeta and a complex between LTBP and unprocessed TGFbeta. We investigated the ability of thrombospondins (TSP1 and TSP2) to activate these latent forms of TGFbeta. TSP1 and TSP2 were equally potent at activating the LTBP-latency-associated protein-TGFbeta

complex in the absence of cell contact, but were ineffective on the alphainf 2M-TGFbeta complex. Therefore, TGFbeta may act as an autocrine regulator of adrenocortical steroidogenic functions. Its activity appears to be controlled by TSPs, the local production of which is regulated by systemic ACTH.

2/AB/21 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

05326096 EMBASE No: 1993094181
The in situ localization of tenascin splice variants and thrombospondin 2 mRNA in the avian embryo
Tucker R.P.
Dept Neurobiol/Anatomy, Neurosci Pro, Bowman Gray School of Medicine, Wake Forest University,Winston-Salem, NC 27157-1010 United States
Development (DEVELOPMENT) (United Kingdom) 1993, 117/1 (347-358)
CODEN: DEVPE ISSN: 0950-1991
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Tenascin and thrombospondin belong to the growing family of extracellular matrix glycoprotein believed to have an anti-adhesive function during development. Immunohistochemistry has been used to identify these proteins in the developing central nervous system, in the matrix surrounding peripheral neurons, and in connective tissue. The antibodies used in most of these studies, however, could not distinguish between different splice variants (tenascin) nor different genetic forms (thrombospondin). For this reason, we used the reverse transcriptase polymerase chain reaction to generate DNA probes that are specific to the transcripts of high M(r) tenascin and thrombospondin 2 . These probes were then used for an in situ hybridization study to determine the cellular origins of specific tenascin and thrombospondin forms throughout the development of the chick. The mRNA encoding high M(r) tenascin was found associated with motile cells and in tissues undergoing dynamic modeling: migrating glia, epithelial glia used as a substratum for migrating neurons, the growing tips of lung buds, and during osteogenesis. In contrast, the mRNAs of low M(r) tenascin were concentrated in areas of cartilage deposition and chondrocyte proliferation. Thrombospondin 2 mRNA was not detected in the developing central nervous system at any time during development by in situ hybridization. In contrast, it was found in embryonic mesenchyme, perichondrium, epimysium, and endothelial cells. Thrombospondin 2 mRNA was detected in poly(A) RNA isolated from embryonic spinal cord and cerebellum by polymerase chain reaction, though it was not detected in poly(A) RNA from the avascular retina. Thus, thrombospondin 2 mRNA may be present in the developing brain at low levels in endothelial cells or blood cells. These data support the notion that tenascin splice variants have distinct roles during development, and that thrombospondin 2 is more likely to be playing a role associated with the morphogenesis of connective tissue than neuronal development.

2/AB/22 (Item 1 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

02501659 4739253
Increased Marrow-Derived Osteoprogenitor Cells and Endosteal Bone Formation in Mice Lacking Thrombospondin 2
Hankenson, K.D.; Bain, S.D.; Kyriakides, T.R.; Smith, E.A.; Goldstein, S.A.

; Bornstein, P.
Dep. Biochem., Univ. Washington, Box 357350, Seattle, WA 98195-7350, USA
Journal of Bone and Mineral Research vol. 15, no. 5, pp. 851-862 (2000)
ISSN: 0884-0431
DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH
SUBFILE: Calcium & Calcified Tissue Abstracts

The phenotype of thrombospondin 2 (TSP2)-null mice includes abnormalities in collagen fibrils and increases in ligamentous laxity, vascular density, and bleeding time. In this study, analyses by computerized tomography (CT) revealed that cortical density was increased in long bones of TSP2 -null mice. Histomorphometric analysis showed that the mid-diaphyseal endosteal bone formation rate (BFR) of TSP2 -null mice was increased in comparison with that of wild-type (WT) animals. Although microgeometric analysis showed that periosteal and endosteal radii were reduced, the mechanical properties of femurs from TSP2 -null mice were not significantly different from those of controls, presumably because of the concomitant increase in endosteal bone mass. Bone loss in ovariectomized mice was equivalent for WT and mutant mice, a finding that indicates that TSP2 -null animals are capable of normal bone resorption. To further explore the cellular basis for the increased endosteal BFR in TSP2 -null mice, marrow stromal cells (MSCs) were isolated and examined in vitro. These cells were found to be present in increased numbers in a colony forming unit (CFU) assay and showed an increased rate of proliferation in vitro. We conclude that TSP2 regulates the proliferation of osteoblast progenitors, directly or indirectly, and that in its absence endosteal bone formation is increased.

2/AB/23 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

15605155 PASCAL No.: 02-0309328
Systemic inhibition of tumor growth and angiogenesis by thrombospondin - 2 using cell-based antiangiogenic gene therapy
STREIT Michael; STEPHEN Antonia E; HAWIGHORST Thomas; MATSUDA Kant; LANGE-ASSCHENFELDT Bernhard; BROWN Lawrence F; VACANTI Joseph P; DETMAR Michael
Cutaneous Biology Research Center and Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown 02129, United States; Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston 02114, United States; Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston 02215, Massachusetts, United States
Journal: Cancer research : (Baltimore), 2002, 62 (7) 2004-2012
Language: English
Recent studies indicate that continuous administration improves the antitumoral efficacy of angiogenesis inhibitors, as compared with intermittent dosing, suggesting a potential role of gene therapy in antiangiogenic tumor therapy. We established a tissue-engineered implant system for the continuous in vivo production of thrombospondin - 2 (TSP - 2), a potent endogenous inhibitor of tumor growth and angiogenesis. Fibroblasts were retrovirally transduced to overexpress TSP - 2 and were seeded onto biodegradable polymer scaffolds. After transplantation into the peritoneal cavity of nude mice, bioimplants maintained high levels of TSP - 2 secretion over extended time periods, resulting in increased levels of circulating TSP - 2 . Bioimplant-generated TSP - 2 potently inhibited tumor growth and angiogenesis of human squamous cell carcinomas, malignant melanomas, and Lewis lung carcinomas that were implanted at a distant site. These results provide the first proof-of-principle for the feasibility and

therapeutic efficiency of systemic, cell-based antiangiogenic gene therapy using biodegradable polymer grafts for the treatment of cancer.

2/AB/24 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

15537670 PASCAL No.: 02-0236165
Control of in vivo microvessel ingrowth by modulation of biomaterial local architecture and chemistry
SANDERS J E; BAKER A B; GOLLEDGE S L
Department of Bioengineering, University of Washington, Seattle, Washington 98195, United States
Journal: Journal of biomedical materials research, 2002, 60 (1) 36-43
Language: English
We developed a method for controlling local architecture and chemistry simultaneously in biomaterial implants to control microvessel ingrowth in vivo. Porous polypropylene disks (5 mm in diameter and 40 mu m thick) were plasma-coated with a fluoropolymer and then laser-drilled with 50- mu m-diameter holes through their thickness. We then oxidized the disks to create hydroxyl functionality on the exposed polypropylene (inside the holes). Acrylamide was grafted to the hydroxyl groups through polymerization in the presence of activating ceric ions. Staining with toluidine blue O demonstrated that grafting occurred only inside the holes. We used the Hoffman degradation reaction to convert the amide groups of acrylamide to amine groups, and then we used ethylene glycol diglycidyl ether to attach biomolecules of interest inside the holes: secreted protein acidic and rich in cysteine (SPARC) peptide Lys-Gly-His-Lys (KGHK; angiogenic), thrombospondin - 2 (TSP; antiangiogenic), or albumin (rat; neutral). In vivo testing in a rat subcutaneous dorsum model for a 3-week interval demonstrated a greater vessel surface area ($p = 0.032$) and a greater number of vessels ($p = 0.043$) in tissue local to the holes with KGHK-immobilized disks than with TSP-immobilized disks. However, differences between KGHK-immobilized and albumin-immobilized disks were less significant ($p = 0.120$ and $p = 0.289$ for the vessel surface area and number of vessels, respectively). The developed methods have potential applications in biomaterial design applications for which selective neovascularization is desired.

2/AB/25 (Item 1 from file: 342)
DIALOG(R)File 342:Derwent Patents Citation Indx

04232331 WPI Acc No: 00-656131/63
Treating a disorder characterized by unwanted cell proliferation e.g. precancerous, cancerous or neoplastic cells or presence of tumor preferably of skin or prostate, comprises increasing thrombospondin-2 activity -
Patent Assignee: (GEHO) GEN HOSPITAL CORP
Author (Inventor): DETMAR M; STREIT M
Patent (basic)
Patent No Kind Date Examiner Field of Search
WO 200057899 A1 001005 (BASIC)
Derwent Week (Basic): 0063
Priority Data: US 127221P (990331)
Applications: AU 200039172 (000324); WO 2000US7835 (000324)

Designated States
(National): AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CR; CU; CZ; DE; DK; DM; DZ; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID ; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL ; TJ; TM; TR; TT; TZ; UA; UG; US; UZ; VN; YU; ZA; ZW
(Regional): AT; BE; CH; CY; DE; DK; EA; ES; FI; FR; GB; GH; GM; GR; IE; IT; KE; LS; LU; MC; MW; NL; OA; PT; SD; SE; SL; SZ; TZ; UG; ZW
Derwent Class: B04; D16
Int Pat Class: A61K-038/16; A61K-038/17; A61K-038/18; A61K-039/395
Number of Patents: 002
Number of Countries: 092
Number of Cited Patents: 000
Number of Cited Literature References: 001
Number of Citing Patents: 000

2/AB/26 (Item 1 from file: 351)
DIALOG(R)File 351:Derwent WPI

013484188
WPI Acc No: 2000-656131/200063
Related WPI Acc No: 2001-465562
XRAM Acc No: C00-198554
Treating a disorder characterized by unwanted cell proliferation e.g. precancerous, cancerous or neoplastic cells or presence of tumor preferably of skin or prostate, comprises increasing thrombospondin - 2 activity
Patent Assignee: GEN HOSPITAL CORP (GEHO); DETMAR M (DETM-I); STEPHEN A E (STEP-I); STREIT M (STRE-I); VACANTI J P (VACA-I)
Inventor: DETMAR M; STREIT M; STEPHEN A E; VACANTI J P
Number of Countries: 093 Number of Patents: 005
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200057899	A1	20001005	WO 2000US7835	A	20000324	200063	B
AU 200039172	A	20001016	AU 200039172	A	20000324	200106	
EP 1171151	A1	20020116	EP 2000918344	A	20000324	200207	
			WO 2000US7835	A	20000324		
US 20020022592	A1	20020221	US 99127221	P	19990331	200221	
			US 2000178842	P	20000127		
			US 2000536087	A	20000324		
			US 2001770339	A	20010126		
			US 2001822161	A	20010330		
KR 2001105403	A	20011128	KR 2001712608	A	20010929	200233	

Priority Applications (No Type Date): US 99127221 P 19990331; US 2000178842 P 20000127; US 2000536087 A 20000324; US 2001770339 A 20010126; US 2001822161 A 20010330
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200057899	A1	E	73	A61K-038/16	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

AU 200039172	A		A61K-038/16	Based on patent WO 200057899
EP 1171151	A1	E	A61K-038/16	Based on patent WO 200057899

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT

LI LT LU LV MC MK NL PT RO SE SI
US 20020022592 A1 A61K-045/00 Provisional application US 99127221
Provisional application US 2000178842
CIP of application US 2000536087
CIP of application US 2001770339
KR 2001105403 A A61K-038/16

Abstract (Basic): WO 200057899 A1
Abstract (Basic):

NOVELTY - Treating (M1) a subject having a disorder characterized by unwanted cell proliferation , comprising increasing thrombospondin - 2 (TSP - 2) activity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) treating (M2) an unwanted skin condition comprising modulating TSP - 2 activity;

(2) diagnosing (M3) a subject at risk of unwanted cell proliferation comprising evaluating the presence of TSP - 2 nucleic acid or its protein; and

(3) identifying (M4) a compound which can be used to treat a disorder characterized by unwanted cell proliferation comprising treating a cell, tissue or subject with a candidate compound, and determining the level of TSP - 2 nucleic acid or its protein, where the ability of the compound to increase TSP - 2 nucleic acid or its protein, indicates that the compound is useful for treating the disorder.

ACTIVITY - Cytostatic; antiinflammatory; antipsoriatic.

MECHANISM OF ACTION - TSP - 2 agonist (claimed); gene therapy. No biological data is given.

USE - To treat a subject having a disorder affecting epithelial tissue characterized by unwanted cell proliferation preferably precancerous, cancerous or neoplastic cells or the presence of tumors preferably of the skin, such as squamous cell carcinoma of the skin or a malignant melanoma, or of the prostate (claimed). The disorder is characterized by benign unwanted skin proliferation, such as psoriasis or papilloma formation (claimed). Evaluating the presence of TSP - 2 nucleic acid or protein is useful for diagnosing the subject at risk for unwanted proliferation such as squamous cell carcinoma, melanoma or prostate cancer.

pp; 73 DwgNo 0/0

?

09/822,682

Set	Items	Description
S1	181	TSP(W)2
S2	5387640	CANCER? OR NEOPLASM? OR TUMOR?
S3	70	S1 AND S2
S4	10	S3 NOT PY=>2000
S5	3	RD (unique items)

Your SELECT statement is:
s tsp(w)2 and cancer

Items	File
9	5: Biosis Previews(R)_1969-2003/Feb W4
10	34: SciSearch(R) Cited Ref Sci_1990-2003/Feb W4
11	71: ELSEVIER BIOBASE_1994-2003/Mar W1
11	73: EMBASE_1974-2003/Feb W4
1	98: General Sci Abs/Full-Text_1984-2003/Jan
3	135: NewsRx Weekly Reports_1995-2003/Feb W2
6	144: Pascal_1973-2003/Feb W3
11	149: TGG Health&Wellness DB(SM)_1976-2003/Feb W3
7	155: MEDLINE(R)_1966-2003/Feb W4
6	159: Cancerlit_1975-2002/Oct
1	172: EMBASE Alert_2003/Mar W1
1	266: FEDRIP_2003/Jan
4	399: CA SEARCH(R)_1967-2003/UD=13809

5/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12340926 BIOSIS NO.: 200000094428
Thrombospondin-2: A potent endogenous inhibitor of tumor **growth and angiogenesis.**
AUTHOR: Streit Michael; Riccardi Lucia; Velasco Paula; Brown Lawrence F; Hawighorst Thomas; Bornstein Paul; Detmar Michael(a)
AUTHOR ADDRESS: (a)Cutaneous Biology Research Center and Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, 02129**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 96 (26):p14888-14893 Dec. 21, 1999
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Recent evidence suggests a potential role for thrombospondin-2 (**TSP - 2**), a matricellular glycoprotein, in the regulation of primary angiogenesis. To directly examine the biological effect of **TSP - 2** expression on **tumor** growth and angiogenesis, human A431 squamous cell carcinoma cells, which do not express **TSP - 2** , were stably transfected with a murine **TSP - 2** expression vector or with vector alone. A431 cells expressing **TSP - 2** did not show an altered growth rate, colony-forming ability, or susceptibility to induction of apoptosis in vitro. However, injection of **TSP - 2** -transfected clones into the dermis of nude mice resulted in pronounced inhibition of **tumor** growth that was significantly stronger than the inhibition observed in A431 clones stably transfected with a thrombospondin-1 (TSP-1) expression vector, and combined overexpression of TSP-1 and **TSP - 2** completely prevented **tumor** formation. Extensive areas of necrosis were observed in **TSP - 2** -expressing **tumors** , and both the density and the size of **tumor** vessels were significantly reduced, although **tumor** cell expression of the major **tumor** angiogenesis factor, vascular endothelial growth factor, was maintained at high levels. These findings establish **TSP - 2** as a potent endogenous inhibitor of **tumor** growth and angiogenesis.

5/9/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11848740 BIOSIS NO.: 199900094849
Thrombospondin 2 expression is correlated with inhibition of angiogenesis and metastasis of colon cancer .
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ABSTRACT: Two subtypes of thrombospondin (TSP-1 and **TSP - 2**) have inhibitory roles in angiogenesis in vitro, although the biological significance of these TSP isoforms has not been determined in vivo. We examined TSP-1 and **TSP - 2** gene expression by reverse transcription polymerase chain reaction (RT-PCR) analysis in 61 colon **cancers** . Thirty-eight of these 61 colon **cancers** were positive for **TSP - 2** expression and showed hepatic metastasis at a significantly lower incidence than those without **TSP - 2** expression (P = 0.02). **TSP - 2** expression was significantly associated with M0 stage in these colon **cancers** (P = 0.03), whereas TSP-1 expression showed no apparent correlation with these factors. The colon **cancer** patients with **TSP - 2** expression showed a significantly low frequency of liver metastasis correlated with the cell-associated isoform of vascular endothelial growth factor (VEGF-189) (P = 0.0006). Vascularity was estimated by CD34 staining, and **TSP - 2** (-)/VEGF-189(+) colon **cancers** showed significantly increased vessel counts and density in the stroma (P < 0.0001), **TSP - 2** (-)VEGF-189(+) colon **cancer** patients also showed significantly poorer prognosis compared with those with **TSP - 2** (+)/VEGF-189(-) (P = 0.0014). These results suggest that colon **cancer** metastasis is critically determined by angiogenesis resulting from the balance between the angioinhibitory factor **TSP - 2** and angiogenic factor VEGF-189.

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Abstract: The thrombospondin (TSP) family of extracellular matrix glycoproteins are widely expressed in the developing and adult central nervous system although their function remains poorly defined, We have used cell culture techniques to analyse the expression and function of TSPs in glial cells derived from myelinated regions of the central nervous system, These experiments show that TSP-1 mRNA, but not **TSP - 2** or TSP-3 mRNA, is expressed by astrocytes from these regions. TSP-1 mRNA levels in astrocytes are under the regulation of growth factors, being increased by TGF beta 1 and decreased by bFGF. Oligodendrocyte precursors do not express TSP-1, **TSP - 2** , or TSP-3 mRNA. Migration of oligodendrocyte precursor cells is stimulated by TSP-1 substrates as measured either by time-lapse microscopy or using a microchemotaxis chamber assay. Taken together, these results suggest that the extracellular matrix molecule TSP-1 plays a role in normal central nervous system development by contributing to the regulation of oligodendrocyte precursor migration. (C) 1997 Wiley-Liss, Inc.
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